clude the sometimes forgotten patient, the public, and other health care professions, medical education and public health.

- The decision-making processes of the AMA for short-range and long-range policy and action with particular consideration of the relation of these processes to the swiftness of professional and social change as it is today and may be anticipated in the next few decades.
- The fact-gathering and the information mechanisms of the AMA upon which scientific, social, economic and political policy and action decisions are made, and whether or not these are accurate and sufficient.
- The organizational structure and machinery for action of the AMA and whether or not these are capable of effectively furthering the association's aims both internally and externally.
- The governance of the AMA and its relationship to its members, its other constituencies if any, other professions in the health field, and public and private health care agencies.

Wesley Hall's suggestion offers a timely opportunity for renewal in the AMA and the chance for that body to play an enormously effective role in the significant years ahead. This opportunity must not be passed up.

—MSMW

Tetanus – The Role of Diazepam in Therapy

A NONFATAL CASE of tetanus in a 12-year-old boy with no previous history of tetanus toxoid injections is presented as the subject of the Specialty Conference in this issue of CALIFORNIA MEDICINE. The present annual incidence of this disease in the United States is only about one case per million population, and a gradual decline in both incidence and mortality rates has occurred over the last 20 years.[1] The age group from 10 to 19 years is especially favored by the statistics, since it has the lowest incidence of any age group in the United States, as well as the lowest case-fatality ratio (16 percent).[2]

Any potential improvement in the therapy of a frequently fatal disease is certainly welcome. The dramatic effects of diazepam on the rigidity and spasms of tetanus have been emphasized in the Specialty Conference and by other observers.[3] Though its exact mode of action is unknown, diazepam appears to depress stimulatory influences of the brain-stem on spinal motor-neurones. Since the major effect of tetanospasmin, the neurotoxin of tetanus, is to block inhibitory influences that act on motor-neurones, diazepam might produce its effect by restoring a more favorable balance between excitatory and inhibitory influences. Regardless of its mode of action, the drug produces a desirable sedative effect, does not produce respiratory depression even when administered in high dosage, and seems superior in its muscle relaxant effects to other tranquilizer drugs, such as chlordiazepoxide, meprobamate, and chlorpromazine, which have also been used in the treatment of tetanus.

Despite the above desirable properties, the effect of the inclusion of diazepam in the treatment of tetanus cases in the United States has not been sufficiently studied to allow any firm conclusions as to its influence on case-fatality ratios of this disease, which remains highly lethal especially for neonates and persons over 50 years of age (in these age groups more than three of every four patients die[1]). The outcome of a case of tetanus depends on many factors of variable importance, and the effect of a specific variable may be difficult to establish except by the analysis of a large number of cases.[1,4] Neither retrospective epidemiologic analysis nor a prospective clinical study of tetanus cases in the United States to evaluate the effect of diazepam on case-fatality ratios has yet been reported. A relatively small effect might be anticipated, however, since patients with frequent paroxysmal spasms that are triggered by both endogenous and exogenous stimuli are unlikely to respond satisfactorily to diazepam, and the treatment of choice in such cases is the induction of total paralysis with curare-type compounds and the provision of total respiratory support. The skill with which these maneuvers and their complications are managed will doubtlessly remain the major determinant of the outcome of severe cases.

It would be unfortunate if the dramatic clinical effects of diazepam led to an under-emphasis of the need for continuous and conscientious at-

tention to the patient, or to a disregard for the importance of other aspects of therapy. Tetanospasmin is presumably slowly metabolized from its binding sites in the nervous system and probably does not cause permanent structural damage. The objectives of therapy are to provide continuous supportive care to the patient while this event is taking place, and to prevent additional toxin from reaching the nervous system by the prompt administration of antitoxin, surgical excision of infected foci, and the use of antibiotics.

Antitoxin is inactive, and antibiotics are unreliable against spores of Clostridium tetani. Since the disease does not induce natural immunity, concurrent active immunization with tetanus toxoid is also indicated. Such immunization is particularly important when the infected site cannot be identified and surgically excised, as is illustrated by the case reported upon herein and nearly 7 percent of all cases in the United States.[1]

The usefulness of diazepam as an adjunctive agent in the management of moderate or mild tetanus cases seems clearly established, but the significance of this drug on the mortality of tetanus among cases in this country has yet to be established.

JOHN V. BENNETT, M.D.
Chief, Bacterial Diseases Branch
Epidemiology Program
Center for Disease Control
Health Services and Mental Health Administration
Public Health Service, Department of Health, Education, and Welfare
Atlanta, Georgia

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Inborn Errors of Metabolism

IT IS NOW NEARLY seventy years since the first publication of Garrod's studies on alkaptonuria[1] opened the field of human biochemical genetics. It is of some interest for the history of medicine and science that these beginnings were clinical, with the careful observations of his patients by a scholarly physician. Garrod coined the term *inborn errors of metabolism* in the title of his book.[2]

These disorders are relatively rarely encountered. However, from the beginning they have been of significance far out of proportion to their incidence. It was from the study of inherited disorders of amino acid metabolism that the idea was first conceived that one gene determines the structure of an enzyme protein.[2] It was also in this context that the concept of genetic determination of human variation was first clearly expressed.[1,2] Elsewhere in this issue of CALIFORNIA MEDICINE, Menkes has reviewed the status in 1971 of the disorders of amino acid metabolism. It is clear that these disorders continue to contribute to our understanding of health and disease.

The rate of discovery of new diseases promises continued excitement in this field. Recently, this has been particularly true for anomalies in the metabolism of the branched chain amino acids, a field of inquiry that was opened by Menkes with his description of maple syrup urine disease. Many of these disorders present with a picture of overwhelming illness very early in life, and if they are undiagnosed or untreated the patients seldom survive the neonatal period. These findings have focused attention on the newborn intensive care unit as a place where more metabolic diseases may be waiting to be discovered than in institutions for the mentally retarded.

The types of methodology employed in this field are changing too. Most of the early discoveries in the inborn errors of metabolism depended on the fact that amino groups react with ninhydrin to produce a readily detected purple color. This is the fundamental principle of the detection of amino acids whether by chromatography on paper or thin layer or by the automatic amino acid analyzer. It is probably true that the major proportion of what can be discovered using the ninhydrin reaction has already been discovered. On the other hand, in the catabolism of most amino acids one of the earliest steps results in the loss of the amino group. Therefore, inborn errors of the subsequent metabolism of these amino acids might make up the majority of such disorders. Their detection